

Wahl der optimalen Therapie – jüngere Patienten



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Multiples Myelom

Hochdosischemotherapie und autologe Stammzelltransplantation

Standard- chemotherapie

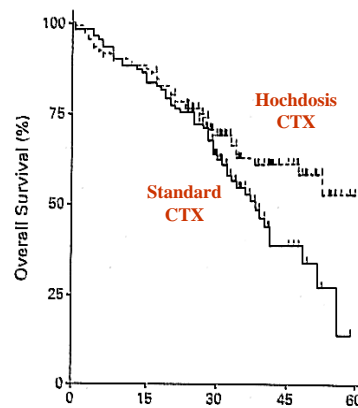
18 Zyklen CTX

Hochdosis- chemotherapie

4 Zyklen CTX →
Hochdosistherapie

Ansprechen

CR	5%	22%
PR	52%	59%
PD	25%	12%

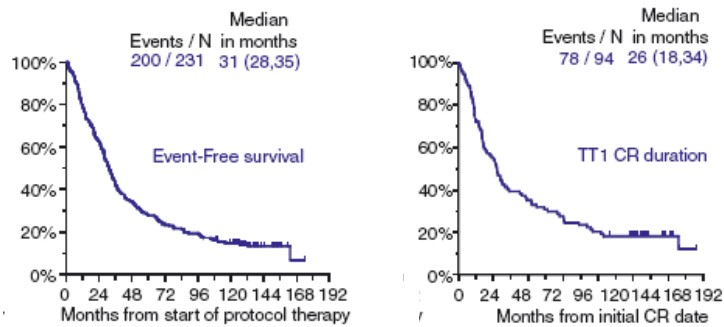


Attal et al., NEJM, 1996

Langzeitergebnisse nach Hochdosis-Melphalan



12 Jahres-follow up des Total Therapy (TT) 1 - Protokolls



OSS: 62/231 (17%) nach 15 Jahren
EFS: 31/231 (7%), davon 12% aller Patienten mit CR

Barlogie et al, BJH 2006

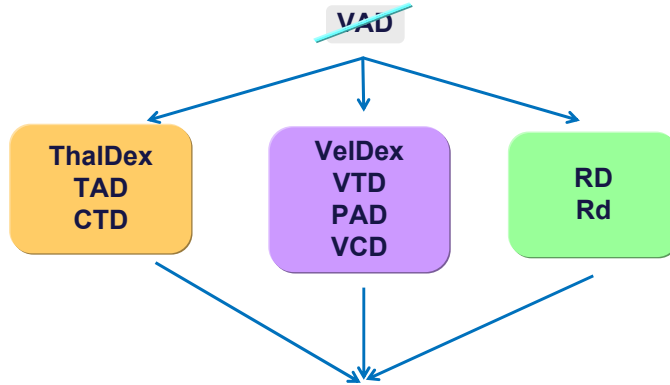
Verbesserung des Ansprechens nach Hochdosistherapie



- VAD war über Jahre hinweg das Standard-Induktionsprotokoll
aber: nur ~10% CR¹
- Höhere CR + VGPR nach autologer SCT: ↑ EFS und OS²
- Ziel: Besseres Ansprechen vor und nach SCT mit “neuen Substanzen”
- Einsatz der neuen Substanzen vor SCT: ↑ CR-Raten ^{2,3}
- Höhere CR + VGPR-Raten nach Induktion: noch bessere Langzeitdaten ? ^{2,4}

1. Reece. Hematology 2005
2. Harousseau. Ann Oncol 2002
3. Attal et al. Hematology 2007
4. Jagannath. Haematologica 2007

Neue Induktionsprotokolle für transplantationsfähige Patienten



Stammzellsammlung →
HD-Melphalan →
Stammzellretransfusion

RD: Lenalidomide + hochdos. Dex
Rd: Lenalidomide + niedriger dos. Dex

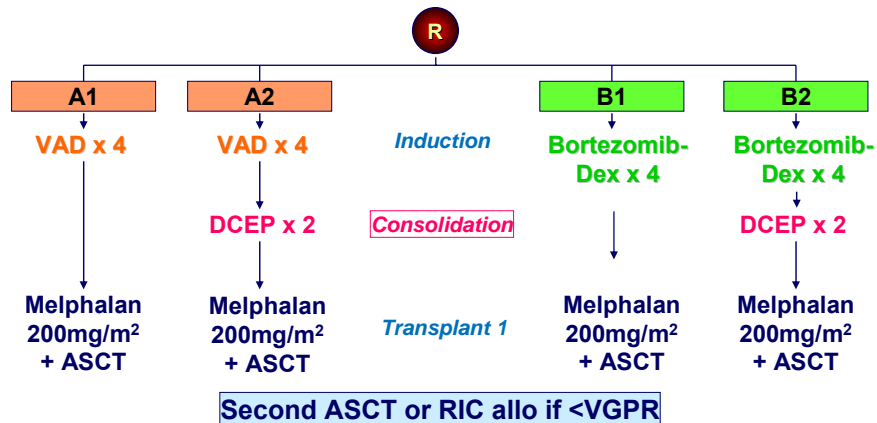
IFM2005/01 Study: VAD versus Bortezomib-Dex



Primary analysis: response to VAD vs Bortezomib-Dex

Randomization stratified by

β_2 -microglobulin level (>3mg/L vs \leq 3mg/L) and presence of chromosome 13 abnormalities (FISH)



Harousseau et al. ASH 2007; ASCO 2008

IFM2005/01 Study: VAD *versus* Bortezomib-Dex



Outcome

	VAD n=219	Bortezomib-Dex n=223	<i>p</i>
CR + nCR	32%	39%	<0.0001
≥VGPR	47%	68%	<0.0001
2-year PFS	60%	69%	0.0115
Median PFS	28 months	Not reached	n.a.
2-year OS	88%	90%	0.4689

Harousseau et al. ASH 2007; ASCO 2008

Molecular classification of multiple myeloma

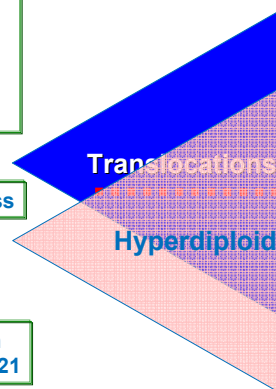


Causative events

Translocations
 t(4;14)
 t(11;14)
 t(6;14)
 t(14;16)
 t(16;20)

Chromosome 13 loss

Chromosome gain
 3, 5, 7, 9, 11, 15, 19, 21



Progression events

Mutation
 Methylation
 Deletion

Chromosome 17p loss

adapted from Bergsagel et al, Blood 2005

Chromosomal abnormalities with prognostic significance



Incidence on interphase FISH

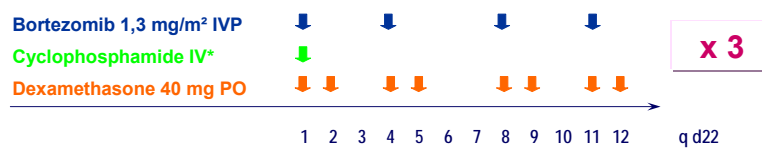
“Good translocations”	t(11;14)	15%
“Bad” translocations	t(4;14) t(14;20) t(14;16)	20%
Deletions	del(13) del(17p) del(1p)	45% 8% 25%
Gains in genetic material	1q+	40%

adapted from Morgan, EMA 2009

DSMM XI Trial: VCD induction



Dose definition for intravenous cyclophosphamide



Cyclo-MTD: 900mg/m², selected from 3 dose levels

DLTs: Leuko-/neutropenia (n=6),
Pneumonia (n=1)

Median TTR: 63 days

PBSC harvest: 28/28 pts (median of 1 apheresis)

Kropff et al., Ann Hematol 2009

Patient characteristics, n=200



Age (mean ± SD) [years]	52.4 ± 6.8
Gender distribution (female/male) [%]	46.5 / 53.5
Durie&Salmon Stages [N (%)]	
- II	49 (24.5)
- III	148 (74.0)
- missing	3 (1.5)
Type of MM [N (%)]	
- IgG/A/D	160 (80.0)
- Light chain myeloma	39 (19.5)
- missing	1 (0.5)
β ₂ -microglobulin [mg/l]	3.75 ± 3.38, range 1.0 – 35.9
Cytogenetic subgroups [n (%)]	
- No FISH abnormalities	51 (25.5)
- 13q-deletion	55 (27.5)
- 17p-deletion	20 (10.0)
- t(4;14)	16 (8.0)
- Missing	40 (20.0)

Knop et al, ASCO 2009

Adverse events, n=200

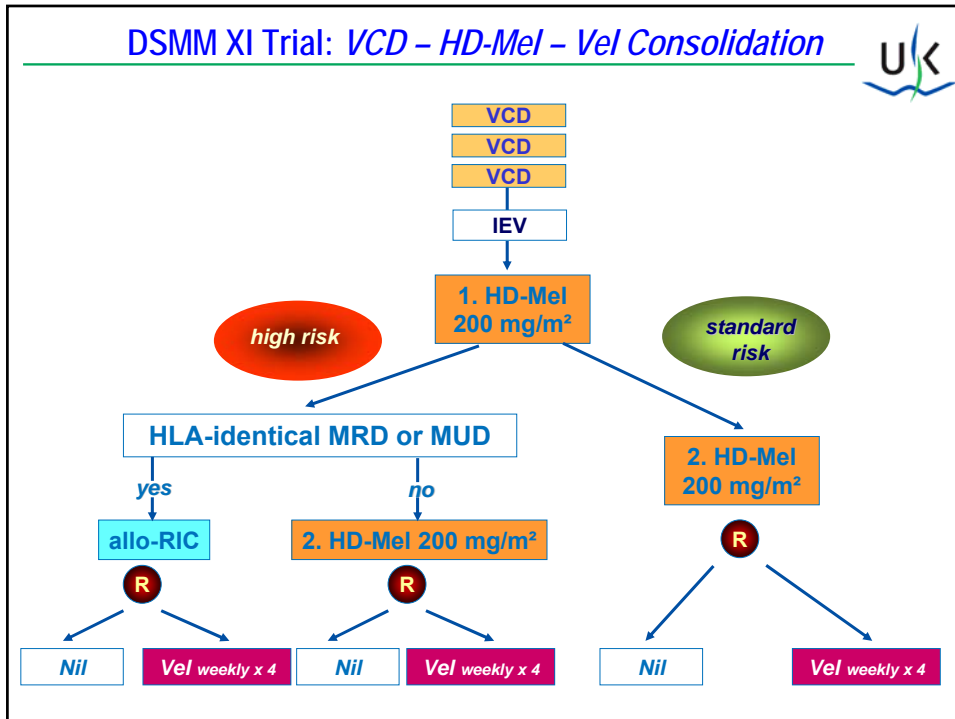


Adverse events	Total [n (%)]	Grade 3 [n (%)]	Grade 4 [n (%)]
Leukopenia	111 (55.5)	43 (21.5)	19 (9.5)
Neutropenia	19 (9.5)	8 (4.0)	5 (2.5)
Thrombocytopenia	74 (37.0)	9 (4.5)	1 (0.5)
Anemia	45 (22.5)	9 (4.5)	1 (0.5)
Nausea	51 (25.5)	4 (2.0)	-
Diarrhea	41 (20.5)	2 (1.0)	-
Constipation	38 (19.0)	-	-
Vomiting	21 (10.5)	4 (2.0)	-
Polyneuropathy	25 (12.5)	1 (0.5)	-
Paraesthesia	44 (22.0)	2 (1.0)	-
Hypoaesthesia	16 (8.0)	1 (0.5)	-
Infections/infestations	94 (47.0)	8 (4.0)	-
Herpes zoster	12 (6.0)	2 (1.0)	-

ITT population, n = 200, according to investigator assessment

Knop et al, ASCO 2009

DSMM XI Trial: VCD – HD-Mel – Vel Consolidation



Response in relation to molecular cytogenetics



Molecular cytogenetics / FISH	Response: CR + PR (assessment by investigator)	
	YES, n (%)	NO, n (%)
Overall, n = 200	168 (84.0)	32 (16.0)
Normal, n = 51	44 (86.3)	7 (13.7)
Abnormalities, n = 91	75 (82.4)	16 (17.6)
13q-, n = 55	45 (81.8)	10 (18.2)
t(4;14), n = 16	15 (93.8)	1 (6.3)
17p-, n = 20	14 (70.0)	6 (30.0)
Other, n = 48	42 (87.5)	6 (12.5)
Unclassifiable, n = 18	15 (83.3)	3 (16.7)
Missing, n = 40	34 (85.0)	6 (15.0)

Novel treatment regimens and adverse cytogenetic abnormalities

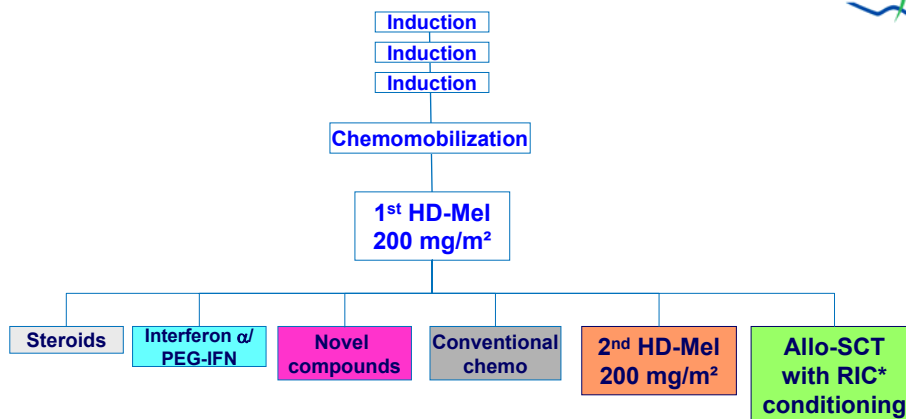


Trial (regimen)	Whole population			del(13)			t(4;14)			del(17p)		
	n	ORR, %	TTP, months	n	ORR, %	TTP, months	n	ORR, %	TTP, months	n	ORR, %	TTP, months
APEX (Bort)	333	38	6	11	20	2.6*	-	-	-	-	-	-
Richardson (RVD)	65	100	-	7	86	-	10	100	-	-	-	-
Avet-Loiseau (Len + Dex)	207	59	9.6	41	43*	5.0*	14	39*	5.5*	-	-	-
MM-016 (Len + Dex)	130	83	7.1	54	76	5.9	28	79	8.0	12	58*	2.2*
Dimopoulos (Len + Dex ± Bort)	48	52	-	-	33	-	-	33	-	-	17*	-
Knop (RAD)	69	73	10.4	15	67	NS	4	50	NS	5	20*	4.6*
Cavo [‡] (VTD)	199	61	-	-	71	-	-	79	-	-	-	-
Knop (VCD)	200	84	-	45	82	-	15	94	-	14	70	-

*indicates significant difference vs no cytogenetic abnormalities; NS = no significant difference; †indicates ≥ VGPR.

Jagannath et al. Leukemia 2007;21:151-7. Richardson et al. Blood 2008;112:[abs 92]; updated data at ASH 08. Avet-Loiseau et al. Blood 2008;112:[abs 3685]; updated data at ASH 08. Bahlis et al. Blood 2008;112:[abs 1731]; updated data at ASH 08. Dimopoulos et al. Blood. 2008;112:[abs 1726]. Knop et al. Blood. 2009 Apr 30. Cavo et al. Blood 2008;112:[abs 1662]. Knop et al. JCO 2009;27:[abs 8516].

Potential Options Following Autologous Stem Cell Transplant



Maintenance

Consolidation

* Reduced intensity conditioning

Thalidomide maintenance studies

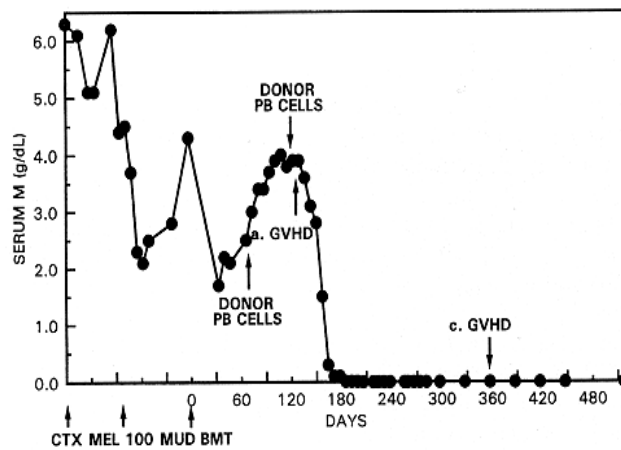


n	Treatment	CR (%)	PFS (%)	OS (%)
668	Double ASCT; Randomization to thal throughout vs no thal; until disease progression	65 vs 43 $p < 0.001$	56 vs 44 (5-year) $p = .01$	65 vs 65 (5-year) n.s.
597	Double ASCT; Pamidronate + thal vs pamidronate vs no maintenance; until disease progression	\geq VGPR: 67 vs 57 vs 55 $p = 0.03$	52 vs 37 vs 36 (3-year) $p < .009$	87 vs 74 vs 77 (4-year) $p < .04$
243	Single ASCT; Prednisolone + thal vs prednisolone; 12 months	Not available	35 vs 25 (3-year) $p = .0003$	86 vs 75 (3-year) $p = .02$
195	Single ASCT + thal vs double ASCT; 6 months	Not available	85 vs 57 (3-year) $p = .02$	85 vs 65 (3-year) $p = .04$

Barlogie et al., N Engl J Med 2006
Attal et al., Blood 2006

Abdelkefi et al., Blood 2008
Spencer et al., JCO 2009

Graft-versus-myeloma-effect



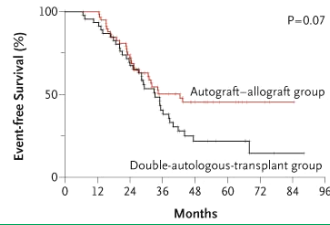
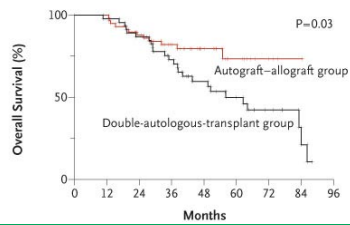
Tricot et al., 1996

Tandem-HD-Melphalan vs. auto-allo-SCT in newly diagnosed MM

The Italian Experience



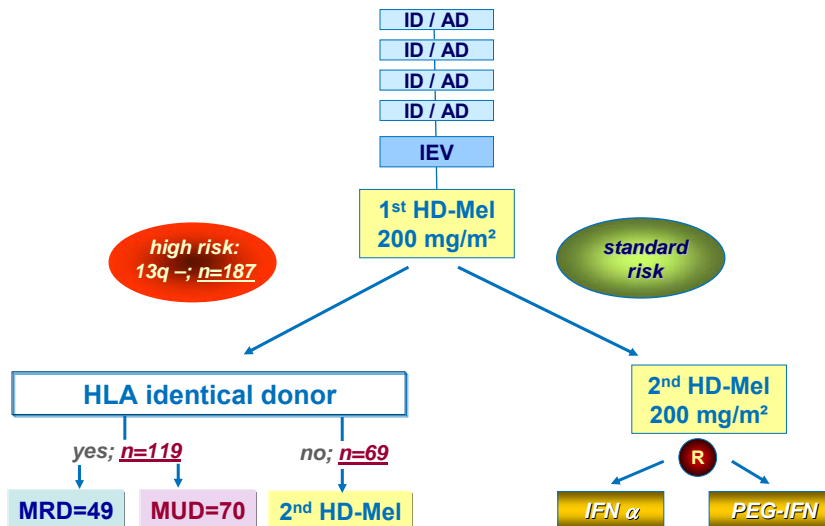
	Tandem-Mel (n=46)	Auto-allo-SCT (n=58)	p
CR rate	26%	55%	.004
ORR	89%	86%	> .05
TRM at 2 years	2%	10%	> .05
Incidence of acute GVHD (°II - IV)	n.a.	43%	n.a.
Relapse mortality	43%	7%	<.001
Medianes OAS n. 46 Mo	58 Mo	n. yet reached	.03



Bruno et al, NEJM 2007

Risk-stratified DSMM V Trial

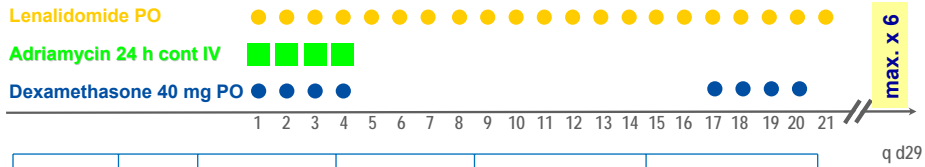
Enrolment onto high-risk group 2/02 - 3/07: n = 187



Lenalidomide-containing regimens in relapsed/refractory MM

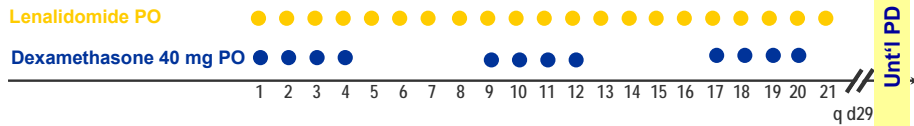


RAD trial



Dose level	Pat. (n)	Lenalidomide	Adriamycin	Dexamethasone	Pegfilgrastim
5+G	45	25 mg d1-21	9 mg/m ² d1-4	40 mg d1-4, d17-20	6 mg; d 6

MM-009 and MM-010



Weber et al., NEJM 2007; Dimopoulos et al., NEJM 2007
Knop et al., Blood 2009

RAD -



Patient characteristics

Patient accrual:

Phase I part	n = 23
Phase II part	n = 46
Total:	n = 69

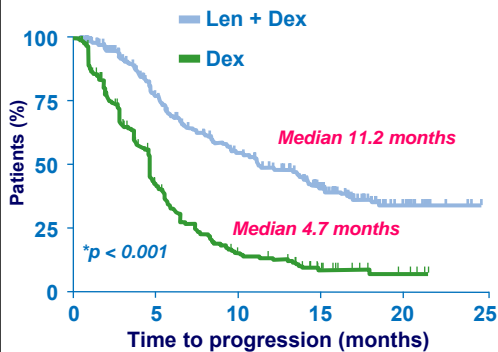
Median age, y (range)	65 (46 - 77)
Median no of prev. therapies (range)	2 (1-3)
Relapsed-refractory disease	32 %
Autologous transplantation (%)	72 %
Auto → allogeneic transplantation (%)	12 %
Any transplant	84 %
Bortezomib	57 %
Thalidomide	20 %
Elevated beta-2-microglobulin, n (%)	29 (42)
Cytogenetic analysis, n (%)	37 (54)
del(13q)	15 (41)
t(4;14)	4 (11)
del(17p)	5 (14)

Knop et al, Blood 2009

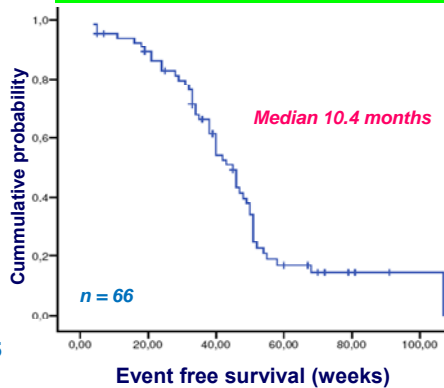
TTP / EFS in lenalidomide-containing trials



MM-009/010 pooled analysis
Median duration of treatment 48 weeks



RAD
Duration of treatment 24 weeks

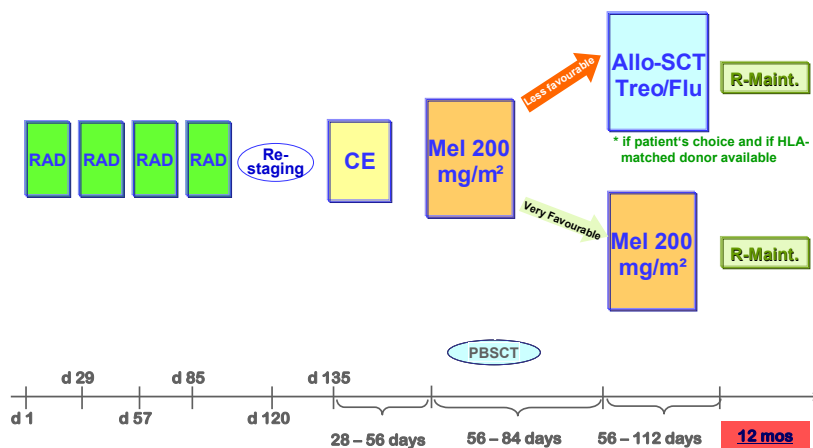


Weber et al., NEJM 2007; Dimopoulos et al., NEJM 2007
Knop et al., Blood, 2009:

RAD as an Induction Treatment in Newly Diagnosed MM



DSMM XII – Trial



... 50 dsmm-Studienzentren

Leitung

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